

PCT

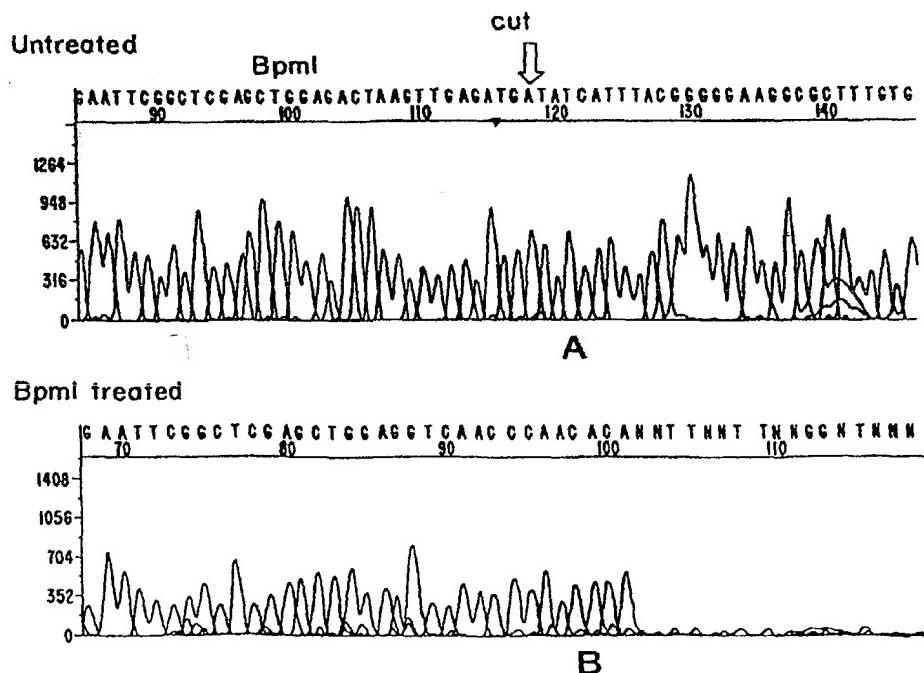
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|--|--------------------------|
| (51) International Patent Classification ⁷ : | A1 | (11) International Publication Number: | WO 00/15833 |
| C12Q 1/44, 1/68, C12P 19/34, C07H 21/04, C12N 9/22 | | (43) International Publication Date: | 23 March 2000 (23.03.00) |
| (21) International Application Number: | | PCT/US99/21092 | |
| (22) International Filing Date: | | 14 September 1999 (14.09.99) | |
| (30) Priority Data: | | | |
| 60/100,491 60/100,704 | 16 September 1998 (16.09.98) 17 September 1998 (17.09.98) | US US | |
| (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications | | | |
| US Filed on US Filed on | 16 September 1998 (16.09.98) 60/100,704 (CIP) 17 September 1998 (17.09.98) | 60/100,491 (CIP) | |
| (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). | | | |
| (72) Inventors; and | | | |
| (75) Inventors/Applicants (for US only): BURNS, Daniel, Keith [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). WEINER, Michael, Phillip [US/US]; Glaxo Wellcome Inc., | | | |

(54) Title: MULTIPLE SEQUENCING METHOD



(57) Abstract

The present invention provides a method for identifying a nucleic acid utilizing a run-off sequencing reaction of a relatively short portion of the nucleic acid. The method can be utilized, for example, to identify an EST from only a small portion of the EST and in an analysis of nucleotide polymorphisms. The figure depicts an untreated and a BpmI-treated sequencing reaction.

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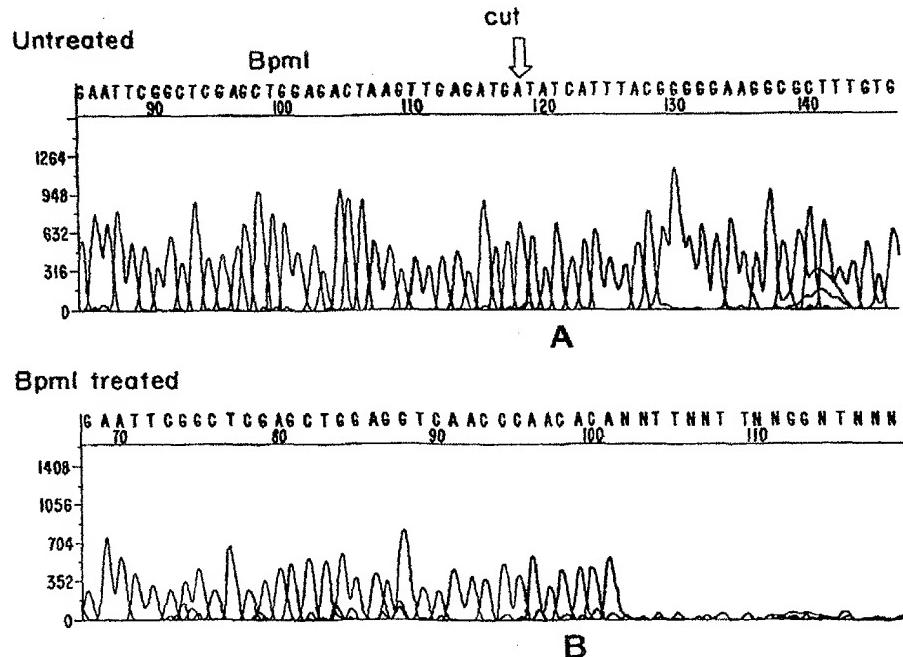
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/21092

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | BRENNER et al. DNA fingerprinting by sampled sequencing. Proceedings of the National Academy of Sciences USA. November 1989, Vol. 86, pages 8902-8906, see entire reference. | 6-12 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/21092

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

USPAT, WPI, JPO, EPO, Medline, CAPLUS, EMBASE, BIOSIS, LIFESCI, SCISEARCH
search terms: sequencing, nucleic acid, dna, polynucleotide, multiple, multi, dual, sequential, run, load, restriction enzyme, restriction endonuclease, BpmI, FokI, BsgI, Eco57I, BcgI, Mmel, AlwI, Alw26I, BbsI, BbvI, BsAI, BsmI, BsmAI, BspMI, Bst71I, Earl, Esp3I, Hgal, HphI, Ksp632I, MbOI, MnII, PteI, SfaNI

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21092

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12Q 1/44, 1/68; C12P 19/34; C07H 21/04; C12N 9/22
US CL :435/6, 19, 91.2, 91.5, 199; 536/24.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 19, 91.2, 91.5, 199; 536/24.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

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| "A" document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" document referring to an oral disclosure, use, exhibition or other means | | |
| "P" document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

01 DECEMBER 1999

Date of mailing of the international search report

04 FEB 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

DIANA B. JOHANNSEN

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference PU3562WO | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 |
| International application No. PCT/US99/21092 | International filing date (day/month/year) 14 SEPTEMBER 1999 | (Earliest) Priority Date (day/month/year) 16 SEPTEMBER 1998 |
| Applicant GLAXO GROUP LIMITED | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (See Box I).
2. Unity of invention is lacking (See Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - transcribed by this Authority.
4. With regard to the title,
 - the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:

Figure No. 1

 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21092

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The technical features mentioned in the abstract do not include a reference sign between parentheses (PCT Rule 8.1(d)).

ABSTRACT

The present invention provides a method for identifying a nucleic acid utilizing a run-off sequencing reaction of a relatively short portion of the nucleic acid. The method can be utilized, for example, to identify an EST from only a small portion of the EST and in an analysis of nucleotide polymorphisms. Figure 1 depicts an untreated and a BpmI-treated sequencing reaction.

INTERNATIONAL SEARCH REPORT

International application No.
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IPC(7) :C12Q 1/44, 1/68; C12P 19/34; C07H 21/04; C12N 9/22
US CL :435/6, 19, 91.2, 91.5, 199; 536/24.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 19, 91.2, 91.5, 199; 536/24.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Box PCT
Washington, D.C. 20231

Authorized officer

DIANA B. JOHANNSEN

Faxsimile No. (703) 305-0736

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/21092

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | BRENNER et al. DNA fingerprinting by sampled sequencing. Proceedings of the National Academy of Sciences USA. November 1989, Vol. 86, pages 8902-8906, see entire reference. | 6-12 |

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International application No.
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Electronic data bases consulted (Name of data base and where practicable terms used):

USPAT, WPI, JPO, EPO, Medline, CAPLUS, EMBASE, BIOSIS, LIFESCI, SCISEARCH
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: DAVID J. LEVY
GLAXO WELLCOME INC.
FIVE MOORE DRIVE
PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

Docket No: PU3562WO
GNA Attorney: ES
Paper: Att. 19 Amendment
Due Date: 3/4/00
Deadline: 4/4/00

Recorded: FEB
Applicant's or agent's file reference

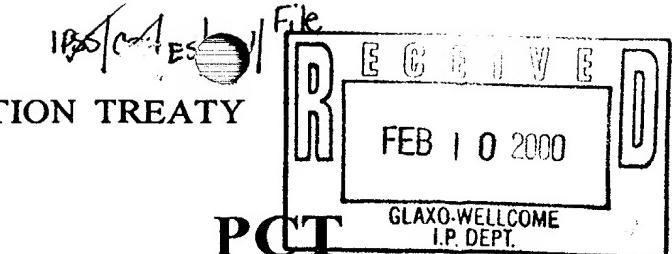
PU3562WO

International application No.

PCT/US99/21092

Applicant

GLAXO GROUP LIMITED



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

04 FEB 2000

FOR FURTHER ACTION See paragraphs 1 and 4 below

International filing date
(day/month/year)

14 SEPTEMBER 1999

1. The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

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Facsimile No. (703) 305-3230

Authorized officer

DIANA B. JOHANNSEN

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: DAVID J. LEVY
GLAXO WELLCOME INC.
FIVE MOORE DRIVE
PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

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|---|---|
| Applicant's or agent's file reference PU3562WO | Date of Mailing (day/month/year) 04 FEB 2000 |
| International application No. PCT/US99/21092 | FOR FURTHER ACTION See paragraphs 1 and 4 below International filing date (day/month/year) 14 SEPTEMBER 1999 |
| Applicant GLAXO GROUP LIMITED | |

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| | |
|---|--|
| Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230 | Authorized officer DIANA B. JOHANNSEN Telephone No. (703) 308-0196 |
|---|--|

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
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Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

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ABSTRACT

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INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

USPAT, WPI, JPO, EPO, Medline, CAPLUS, EMBASE, BIOSIS, LIFESCI, SCISEARCH
search terms: sequencing, nucleic acid, dna, polynucleotide, multiple, multi, dual, sequential, run, load, restriction enzyme, restriction endonuclease, BpmI, FokI, BsgI, Eco57I, BcgI, MmeI, AlwI, Alw26I, BbsI, BbvI, BsaI, BsmI, BsmAI, BspMI, Bst71I, Earl, Esp3I, HgaI, HphI, Ksp632I, MboII, MnlI, PstI, SfaNI

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|--|--|
| Date of mailing (day/month/year) 09 May 2000 (09.05.00) | |
| International application No. PCT/US99/21092 | Applicant's or agent's file reference PU3562WO |
| International filing date (day/month/year) 14 September 1999 (14.09.99) | Priority date (day/month/year) 16 September 1998 (16.09.98) |
| Applicant BURNS, Daniel, Keith et al | |

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

17 March 2000 (17.03.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|--|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Diana Nissen Telephone No.: (41-22) 338.83.38 |
|---|--|

PATENT COOPERATION TREATY

PCT

REC'D 05 JAN 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT

(PCT Article 36 and Rule 70)

| | | |
|--|---|---|
| Applicant's or agent's file reference PU3562WO | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US99/21092 | International filing date (day/month/year) 14 SEPTEMBER 1999 | Priority date (day/month/year) 16 SEPTEMBER 1998 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant GLAXO GROUP LIMITED | | |

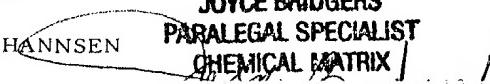
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|--|---|
| Date of submission of the demand 17 MARCH 2000 | Date of completion of this report 29 NOVEMBER 2000 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer DIANA JOHANNSEN  JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/21092

I. Basis of the report

1. With regard to the elements of the international application:*

 the international application as originally filed the description:

pages 1-7, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

 the claims:

pages 8-9, as originally filed
 pages NONE, as amended (together with any statement) under Article 19
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

 the drawings:

pages 1-4, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

 the sequence listing part of the description:

pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in printed form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages NONE
- the claims, Nos. NONE
- the drawings, sheets/fig. NONE

5. This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** The replacement sheet containing the amendment(s) referred to in the preceding footnote must be submitted to the International Bureau in accordance with Rule 70.16.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/21092

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

| | | |
|--------------------------------------|--------------------|-----|
| Novelty (N) | Claims <u>1-18</u> | YES |
| | Claims <u>NONE</u> | NO |
| Inventive Step (IS) | Claims <u>1-12</u> | YES |
| | Claims <u>18</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-18</u> | YES |
| | Claims <u>NONE</u> | NO |

2. citations and explanations (Rule 70.7)

Claim 18 lacks an inventive step under PCT Article 33(3) as being obvious over Kinzler et al (U.S. Patent No. 5,695,937).

The claim is drawn to a kit comprising "an enzyme that cuts at least 1 base downstream of a selected enzyme recognition site" and a "set of oligonucleotide linkers comprising a recognition site for the selected enzyme". It is noted that the intended use of a product such as a kit is not accorded patentable weight. Kinzler et al teach a method for the "serial analysis of gene expression" that requires the use of type IIS restriction enzymes and oligonucleotide linkers comprising recognition sites for type IIS restriction enzymes (see entire reference). Kinzler et al teach kits comprising sets of linkers wherein the linkers "comprise a restriction endonuclease site for cleavage of DNA at a site distant from the restriction endonuclease recognition site" (col 8, lines 1-18). Kinzler et al further teach the use of type IIS restriction enzymes, and teach that such enzymes cleave "at a site distant from or outside of the recognition site" that is "up to 20 bp away from their asymmetric recognition sites" (col 5, lines 51-60). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the kits of Kinzler et al so as to have included in the kits both oligonucleotide linkers and type IIS restriction enzymes that recognize the recognition sites present in the linkers, as well as other reagents required for the practice of Kinzler et al's method. As both the linkers and the restriction enzymes are necessary for the practice of Kinzler et al's method, an ordinary artisan would have been motivated to have made such a modification in order to have provided practitioners with all the reagents necessary to carry out the method of Kinzler et al, for the advantages of convenience, efficiency, and cost-effectiveness.

Claims 1-12 meet the criteria set out in PCT Article 33(2)-(4). Schellenberg et al (U.S. Patent No. 5,449,604) disclose "multiple loading of gel lanes" with different PCR samples (col 36, lines 39-45). Grossman et al (U.S. Patent No. 5,374,527) teach sequencing of short DNA fragments (col 3, line 67-col 4, line 2. (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/21092

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-13 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s).

Claims 1-6 are indefinite for failing to recite a final process step that clearly relates back to the preamble. The claims are drawn to a method "of identifying a nucleic acid", yet recite a final process step of loading sequencing reaction products onto a sequencing gel. The claims do not set forth how loading "two or more" short sequencing products allows one to "identify" a nucleic acid. Thus, it is unclear as to whether the claims are intended to be drawn to a method of loading or running a sequencing gel, or to methods of "identifying" a nucleic acid. Further, the term "identifying" is vague and indefinite, as it does not apprise one of skill in the art as to what information is to be ascertained with respect to a nucleic acid. Further, it is unclear as to whether the term "identifying" may encompass solely mental steps of "identification", or whether this language is limited to active method steps. The claims should be amended so as to clarify the actual, active process steps necessary to accomplish "identification" of a nucleic acid.

Claims 1-6 are indefinite over the recitation of the phrases "two or more short sequencing reaction products", "a first sequencing reaction product", and "a second short sequencing reaction product" in claim 1. It is unclear as to whether Applicant intends for the term "first sequencing reaction product" to refer to one of the "two or more short sequencing reaction products", or to another, additional "sequencing reaction product". Thus, it is further unclear as to whether the instant claims require one or more additional "short sequencing reaction products" in addition to the "first sequencing reaction product" and the "second short sequencing reaction product". Clarification is required.

Claims 2-3 are indefinite over the recitation of the phrase "the sequencing reaction product". Claim 1, from which claims 2-3 depend, recites more than one "sequencing reaction product". Accordingly, it is unclear as to how claim 2-3 are intended to modify claim 1 (i.e., do the claims limit each reaction product, the "first sequencing reaction product", the "second short sequencing reaction product"?).

Claims 6-12 are indefinite for failing to recite a final process step that clearly relates back to the preamble. The claims are drawn to a "method of determining the nucleotide sequence of a selected portion of a nucleic acid", yet recite a final process step of "analyzing the first sequencing reaction (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/21092**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C12Q 1/44, 1/68; C12P 19/34; C07H 21/04; C12N 9/22. and US Cl.: 435/6, 19, 91.2, 91.5, 199; 536/24.2

V. 2. REASoNED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

col 12, lines 29-30, col 13, lines 56-59). However, the prior art does not teach or fairly suggest loading multiple short sequencing reaction products "onto the same lanes of a sequencing gel", as required by instant claims 1-6. Sapolsky et al (U.S. Patent No. 5,710,000) disclose methods for "capturing" oligonucleotide sequences adjacent to type IIS restriction sites, and disclose that the sequences of captured oligonucleotides are preferably determined by hybridization (see entire reference). Brenner discloses a DNA fingerprinting method in which termini of fragments generated by digestion with type IIS restriction enzymes are sequenced (see entire reference). However, the prior art does not teach or fairly suggest isolating a nucleic acid from a library comprising a recognition site of an "enzyme that cuts at least 1 base downstream of the recognition site, wherein the recognition site is positioned within 1 base" of an insert, amplifying and digesting the nucleic acid, and subsequently "performing a run-off sequencing reaction utilizing a primer that hybridizes to a region" at or upstream of the recognition site, as required by instant claims 7-12.

----- NEW CITATIONS -----

NONE

VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):

product". The claims do not set forth how "analyzing" a sequencing reaction product results in "determining the nucleotide sequence" of a portion of a nucleic acid, and the term "analyzing" is sufficiently broad so as to encompass solely mental steps of "analysis". Accordingly, it is not clear whether the instant claims are intended to be drawn to methods of determining the sequence of a portion of a nucleic acid, or to methods of "analyzing" a sequencing reaction product. Clarification is required.

Claims 6-13 are indefinite over the recitation of the term "selected enzyme" in claims 6, 8, and 13, and the term "selected portion" in claim 6. It is unclear as to how the term "selected" is intended to modify the structure and/or function of an enzyme or of a "portion". In other words, how would a "selected" enzyme or portion differ from an enzyme or portion? Clarification is required.

Claims 6-12 are indefinite over the recitation of the phrase "the inserts of the library" in claim 6. There is insufficient antecedent basis for this limitation in the claims, as claim 6 does not previously refer to "inserts" of a library.

Claim 7 is indefinite over the recitation of the phrase "analyzed sequentially on the same analysis run". First, it is unclear as to what is encompassed by the language "analyzed sequentially", and as to what actual methods steps might be required in order to accomplish "sequential analysis". Second, there is insufficient antecedent basis for the limitation "the same analysis run", as the claims do not previously refer to an "analysis run" or to a "same analysis run". Clarification is required.

Claim 9 is indefinite over the recitation of the limitation "the selected restriction enzyme". There is insufficient antecedent basis for this limitation in the claims, as the claims do not previously refer to a "selected restriction enzyme".

Claims 10-12 are indefinite over the recitation of the limitation "the analysis...." in each of the claims. It is unclear as to how these limitations on the "analyzing" step of the method result in or otherwise contribute to "determining the nucleotide sequence" of a portion of a nucleic acid. The claims should be amended so as to clarify what actual steps are carried out, and so as to set forth how such steps result in sequence determination.

IPSS/ES/GN

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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JAN 05 2001

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01/05/01

PCT

To: DAVID J. LEVY
GLAXO WELLCOME INC.
GLOBAL INTELLECTUAL PROPERTY DEPT.
FIVE MOORE DRIVE
PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

29 DEC 2000

Applicant's or agent's file reference

PU5562WO

IMPORTANT NOTIFICATION

International application No.

PCT/US99/21092

International filing date (day/month/year)

14 SEPTEMBER 1999

Priority Date (day/month/year)

16 SEPTEMBER 1998

Applicant

GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Faxsimile No. (703) 305-3230

Authorized officer

DIANA JOHANNSEN

Telephone No. (703) 308-0196

JOYCE BRIDGES
PARALEGAL SPECIALIST
CHEMICAL MATRIX

IPSO/ES/6N

PATENT COOPERATION TREATY

RECEIVED

JAN 05 2001

PCT

UNIVERSAL INTELLECTUAL PROPERTY

INTERNATIONAL PRELIMINARY EXAMINATION REPORT LOGGED IN

(PCT Article 36 and Rule 70)

pd 01/05/01

| | | |
|--|---|---|
| Applicant's or agent's file reference PU3562WO | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US98/21092 | International filing date (day/month/year) 14 SEPTEMBER 1998 | Priority date (day/month/year) 16 SEPTEMBER 1998 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant GLAXO GROUP LIMITED | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|--|--|
| Date of submission of the demand 17 MARCH 2000 | Date of completion of this report 29 NOVEMBER 2000 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer DIANA JOHANNSEN JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX Telephone No. (703) 508-0166 |
| Facsimile No. (703) 505-3230 | |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/21092

I. Basis of the report

1. With regard to the elements of the international application:*

 the international application as originally filed the description:

pages 1-7

pages NONE

pages NONE

, as originally filed

, filed with the demand

 the claims:

pages 8-9

pages NONE

pages NONE

pages NONE

, as originally filed

, filed with the demand

 the drawings:

pages 1-4

pages NONE

pages NONE

, as originally filed

, filed with the demand

 the sequence listing part of the description:

pages NONE

pages NONE

pages NONE

, as originally filed

, filed with the demand

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language _____ which is:

 the language of a translation furnished for the purposes of international search (under Rule 23.1(b)). the language of publication of the international application (under Rule 48.3(b)). the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

 contained in the international application in printed form. filed together with the international application in computer readable form. furnished subsequently to this Authority in written form. furnished subsequently to this Authority in computer readable form. The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished. The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. The amendments have resulted in the cancellation of: the description, pages NONE the claims, Nos. NONE the drawings, sheets/fig NONE5. This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendment must be referred to in the International Preliminary Examination Report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/21092

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

| | | |
|-------------------------------|--------------------|-----|
| Novelty (N) | Claims <u>1-19</u> | YES |
| | Claims <u>NONE</u> | NO |
| Inventive Step (IS) | Claims <u>1-12</u> | YES |
| | Claims <u>19</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-19</u> | YES |
| | Claims <u>NONE</u> | NO |

2. citations and explanations (Rule 70.7)

Claim 19 lacks an inventive step under PCT Article 33(3) as being obvious over Kinzler et al (U.S. Patent No. 5,695,937).

The claim is drawn to a kit comprising "an enzyme that cuts at least 1 base downstream of a selected enzyme recognition site" and a "set of oligonucleotide linkers comprising a recognition site for the selected enzyme". It is noted that the intended use of a product such as a kit is not accorded patentable weight. Kinzler et al teach a method for the "serial analysis of gene expression" that requires the use of type IIS restriction enzymes and oligonucleotide linkers comprising recognitions sites for type IIS restriction enzymes (see entire reference). Kinzler et al teach kits comprising sets of linkers wherein the linkers "comprise a restriction endonuclease site for cleavage of DNA at a site distant from the restriction endonuclease recognition site" (col 8, lines 1-18). Kinzler et al further teach the use of type IIS restriction enzymes, and teach that such enzymes cleave "at a site distant from or outside of the recognition site" that is "up to 20 bp away from their asymmetric recognition sites" (col 5, lines 51-60). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the kits of Kinzler et al so as to have included in the kits both oligonucleotide linkers and type IIS restriction enzymes that recognize the recognition sites present in the linkers, as well as other reagents required for the practice of Kinzler et al's method. As both the linkers and the restriction enzymes are necessary for the practice of Kinzler et al's method, an ordinary artisan would have been motivated to have made such a modification in order to have provided practitioners with all the reagents necessary to carry out the method of Kinzler et al, for the advantages of convenience, efficiency, and cost-effectiveness.

Claims 1-12 meet the criteria set out in PCT Article 33(2)-(4). Schellenberg et al (U.S. Patent No. 5,449,604) disclose "multiple loading of gel lanes" with different PCR samples (col 36, lines 39-45). Grossman et al (U.S. Patent No. 5,374,527) teach sequencing of short DNA fragments (col 3, line 67-col 4, line 2, (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/21092

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-15 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s).

Claims 1-6 are indefinite for failing to recite a final process step that clearly relates back to the preamble. The claims are drawn to a method "of identifying a nucleic acid", yet recite a final process step of loading sequencing reaction products onto a sequencing gel. The claims do not set forth how loading "two or more" short sequencing products allows one to "identify" a nucleic acid. Thus, it is unclear as to whether the claims are intended to be drawn to a method of loading or running a sequencing gel, or to methods of "identifying" a nucleic acid. Further, the term "identifying" is vague and indefinite, as it does not apprise one of skill in the art as to what information is to be ascertained with respect to a nucleic acid. Further, it is unclear as to whether the term "identifying" may encompass solely mental steps of "identification", or whether this language is limited to active method steps. The claims should be amended so as to clarify the actual, active process steps necessary to accomplish "identification" of a nucleic acid.

Claims 1-6 are indefinite over the recitation of the phrases "two or more short sequencing reaction products", "a first sequencing reaction product", and "a second short sequencing reaction product" in claim 1. It is unclear as to whether Applicant intends for the term "first sequencing reaction product" to refer to one of the "two or more short sequencing reaction products", or to another, additional "sequencing reaction product". Thus, it is further unclear as to whether the instant claims require one or more additional "short sequencing reaction products" in addition to the "first sequencing reaction product" and the "second short sequencing reaction product". Clarification is required.

Claims 2-3 are indefinite over the recitation of the phrase "the sequencing reaction product". Claim 1, from which claims 2-3 depend, recites more than one "sequencing reaction product". Accordingly, it is unclear as to how claim 2-3 are intended to modify claim 1 (i.e., do the claims limit each reaction product, the "first sequencing reaction product", the "second short sequencing reaction product"?).

Claims 6-12 are indefinite for failing to recite a final process step that clearly relates back to the preamble. The claims are drawn to a "method of determining the nucleotide sequence of a selected portion of a nucleic acid", yet recite a final process step of "analyzing the first sequencing reaction (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/21092

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C12Q 1/44, 1/68; C12P 19/34; C07H 21/04; C12N 9/22. and US Cl.: 435/6, 19, 91.2, 91.5, 199; 536/24.2

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

col 12, lines 29-30, col 13, lines 56-59). However, the prior art does not teach or fairly suggest loading multiple short sequencing reaction products "onto the same lanes of a sequencing gel", as required by instant claims 1-6. Sapolksy et al (U.S. Patent No. 5,710,000) disclose methods for "capturing" oligonucleotide sequences adjacent to type IIS restriction sites, and disclose that the sequences of captured oligonucleotides are preferably determined by hybridization (see entire reference). Brenner discloses a DNA fingerprinting method in which termini of fragments generated by digestion with type IIS restriction enzymes are sequenced (see entire reference). However, the prior art does not teach or fairly suggest isolating a nucleic acid from a library comprising a recognition site of an "enzyme that cuts at least 1 base downstream of the recognition site, wherein the recognition site is positioned within 1 base" of an insert, amplifying and digesting the nucleic acid, and subsequently "performing a run-off sequencing reaction utilizing a primer that hybridizes to a region" at or upstream of the recognition site, as required by instant claims 7-12.

----- NEW CITATIONS -----

NONE

VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):

product". The claims do not set forth how "analyzing" a sequencing reaction product results in "determining the nucleotide sequence" of a portion of a nucleic acid, and the term "analyzing" is sufficiently broad so as to encompass solely mental steps of "analysis". Accordingly, it is not clear whether the instant claims are intended to be drawn to methods of determining the sequence of a portion of a nucleic acid, or to methods of "analyzing" a sequencing reaction product. Clarification is required.

Claims 6-13 are indefinite over the recitation of the term "selected enzyme" in claims 6, 8, and 13, and the term "selected portion" in claim 6. It is unclear as to how the term "selected" is intended to modify the structure and/or function of an enzyme or of a "portion". In other words, how would a "selected" enzyme or portion differ from an enzyme or portion? Clarification is required.

Claims 6-12 are indefinite over the recitation of the phrase "the inserts of the library" in claim 6. There is insufficient antecedent basis for this limitation in the claims, as claim 6 does not previously refer to "inserts" of a library.

Claim 7 is indefinite over the recitation of the phrase "analyzed sequentially on the same analysis run". First, it is unclear as to what is encompassed by the language "analyzed sequentially", and as to what actual methods steps might be required in order to accomplish "sequential analysis". Second, there is insufficient antecedent basis for the limitation "the same analysis run", as the claims do not previously refer to an "analysis run" or to a "same analysis run". Clarification is required.

Claim 9 is indefinite over the recitation of the limitation "the selected restriction enzyme". There is insufficient antecedent basis for this limitation in the claims, as the claims do not previously refer to a "selected restriction enzyme".

Claims 10-12 are indefinite over the recitation of the limitation "the analysis...." in each of the claims. It is unclear as to how these limitations on the "analyzing" step of the method result in or otherwise contribute to "determining the nucleotide sequence" of a portion of a nucleic acid. The claims should be amended so as to clarify what actual steps are carried out, and so as to set forth how such steps result in sequence determination.

PCT**REQUEST**

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) PU3562WO

Box No. I TITLE OF INVENTION
MULTIPLEX SEQUENCING METHOD
Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Glaxo Group Limited

Glaxo Wellcome House

Berkeley Avenue

Greenford, Middlesex

UB6 0NN

GB

 This person is also inventor.Telephone No.
919-483-2370Facsimile No.
919-483-7988

Teleprinter No.

State (that is, country) of nationality:
GBState (that is, country) of residence:
GB

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BURNS, Daniel Keith

c/o Glaxo Wellcome Inc.

Five Moore Drive, PO Box 13398

Research Triangle Park, NC 27709

US

This person is:

 applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

 Further applicants and/or (further) inventors are indicated on a continuation sheet.**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

 agent common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Telephone No.

919-483-2370

LEVY, David, J.; DADSWELL, Charles, E.; GRASSLER, Frank P.; BRINK, Robert H.; RIEK, James P.; PRUS, Karen L.; SELBY, Elizabeth; MORGAN, Lorie Ann; BENNETT, Virginia C.; ROGERS, Christopher P.; all Glaxo Wellcome Inc., Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709-3398, US

Facsimile No.

919-483-7988

Teleprinter No.

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)**If none of the following sub-boxes is used, this sheet is not to be included in the request.**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WEINER, Michael Phillip
c/o Glaxo Wellcome Inc.
Five Moore Drive, PO 13398
Research Triangle Park, NC 27709
US

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

[] Further applicants and/or further inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of
- EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (*if other kind of protection or treatment desired, specify on dotted line*)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IS Iceland | Continuation-in-part |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KR Republic of Korea | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- TZ United Republic of Tanzania
- DM Dominica
- CR Costa Rica

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (*Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the following Office within the 15 month time limit:*)

Supplemental Box*If the Supplemental Box is not used, this sheet need not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) **if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;**
- (ii) **if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;**
- (iii) **if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;**
- (iv) **if, in addition to the agent(s) indicated in Box IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;**
- (v) **if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V., the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;**
- (vi) **if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;**
- (vii) **if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.**

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box IV:

HESKETH, Alan (GB); CRAWLEY, Karen (GB); DOLTON, Peter I. (GB); DAWSON, Hugh B. (GB); FILLER, Wendy Anne. (GB); HACKETT, Ruth Elizabeth (GB); HAMMETT, Audrey G. C. (GB); LANE, Graham M. H. (GB); LEAROYD, Stephanie Anne (GB); QUILLIN, Helen Kaye (GB); REED, Michael A. (GB); REES, Marion (GB); STOTT, Michael John (GB) TEUTEN, Andrew J. (GB); THORNLEY, Rachel M. (GB) and VOLCKMAN, Janis Florence (GB) all in c/o Glaxo Wellcome plc., Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, GB

Continuation of Box V

United States of America: Provisional 60/100,491; 16 September 1998 (16/09/98)

United States of America: Provisional 60/100,704; 17 September 1998 (17/09/98)

| Box No. VI PRIORITY CLAIM | | <input type="checkbox"/> Further priority claims are indicated in the Supplemental Box. | | |
|---|----------------------------------|---|--|--|
| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: | | |
| | | national application: country | regional application: regional Office | international application: receiving Office |
| item (1) 16/09/98 16 September 1998 | 60/100,491 | US | | |
| item (2) 17/09/98 17 September 1998 | 60/100,704 | US | | |
| item (3) | | | | |

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1) (2)
* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

| | | | |
|--|--|--------|------------------------------|
| Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): | Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): | | |
| | Date (day/month/year) | Number | Country (or regional Office) |

ISA/us

Box No. VIII CHECK LIST: LANGUAGE OF FILING

| | | |
|---|--|--|
| This international application contains the following number of sheets: | This international application is accompanied by the item(s) marked below: | |
| request : 5 | 1. <input checked="" type="checkbox"/> fee calculation sheet | |
| description (excluding sequence listing part) : 7 | 2. <input checked="" type="checkbox"/> separate signed power of attorney | |
| claims : 2 | 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | |
| abstract : 1 | 4. <input checked="" type="checkbox"/> statement explaining lack of signature | |
| drawings : 3 | 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as items(s): | |
| sequence listing part of description : 0 | 6. <input type="checkbox"/> translation of international application into (language): | |
| Total number of sheets : 18 | 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material | |
| | 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form | |
| | 9. <input checked="" type="checkbox"/> other (specify): copy of POA giving DJL right to sign for Glaxo Group Limited | |

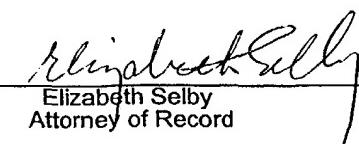
Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application:

English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


 Elizabeth Selby
 Attorney of Record

| | | |
|---|--|--|
| For receiving Office use only | | 2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: |
| 1. Date of actual receipt of the purported international application: | | |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: | | |
| 4. Date of timely receipt of the required corrections under PCT Article 11(2): | | |
| 5. International Searching Authority (if two or more are competent): ISA/ | | |
| 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid | | |

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|--|--|---|-------------------------------------|----------------------------------|---------------------------------|-------------------------------|--|---|---|--|--------|---|-------------|----------|---|----------------------------|--|--|----------|---|-------|---|----------|-------|
| Applicant's or agent's file reference | PU3562WO | Date stamp of the receiving Office | | | | | | | | | | | | | | | | | | | | | | | |
| <p>Applicant Glaxo Group Limited</p> | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p>CALCULATION OF PRESCRIBED FEES</p> | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1. TRANSMITTAL FEE | 240.00 | T | | | | | | | | | | | | | | | | | | | | | | | |
| 2. SEARCH FEE | 700.00 | S | | | | | | | | | | | | | | | | | | | | | | | |
| International search to be carried out by ISA/US | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)</i> | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p>3. INTERNATIONAL FEE</p> <p>Basic Fee</p> <p>The international application contains <u>18</u> sheets.</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 40%;">first 30 sheets</td> <td style="width: 10%; text-align: right;">455.00</td> <td style="width: 10%; text-align: center; border: 1px solid black; padding: 2px;">b₁</td> </tr> <tr> <td><u>0</u> x <u>\$0.00</u></td> <td style="text-align: right;"><u>0.00</u></td> <td style="text-align: center; border: 1px solid black; padding: 2px;">b₂</td> </tr> <tr> <td>remaining sheets additional amount</td> <td colspan="2"></td> </tr> </table> <p>Add amounts entered at b₁ and b₂ and enter total at B</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 40%; text-align: right;">455.00</td> <td style="width: 10%; text-align: center; border: 1px solid black; padding: 2px;">B</td> </tr> </table> <p>Designation Fees</p> <p>The international application contains <u>104</u> designations.</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 40%;">10 x 105.00</td> <td style="width: 10%; text-align: right;">1,050.00</td> <td style="width: 10%; text-align: center; border: 1px solid black; padding: 2px;">D</td> </tr> <tr> <td>number of designation fees</td> <td colspan="2">amount of designation fee payable (maximum 10)</td> </tr> </table> <p>Add amounts entered at B and D and enter total at I</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 40%; text-align: right;">1,505.00</td> <td style="width: 10%; text-align: center; border: 1px solid black; padding: 2px;">I</td> </tr> </table> <p><i>(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled,</i></p> <p>4. FEE FOR PRIORITY DOCUMENT (<i>if applicable</i>)</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 40%; text-align: right;">30.00</td> <td style="width: 10%; text-align: center; border: 1px solid black; padding: 2px;">P</td> </tr> </table> <p>5. TOTAL FEES PAYABLE</p> <p>Add amounts entered at T, S, I and P, and enter total in the TOTAL box</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 40%; text-align: right;">2,475.00</td> <td style="width: 10%; text-align: center; border: 1px solid black; padding: 2px;">TOTAL</td> </tr> </table> | | | first 30 sheets | 455.00 | b ₁ | <u>0</u> x <u>\$0.00</u> | <u>0.00</u> | b ₂ | remaining sheets additional amount | | | 455.00 | B | 10 x 105.00 | 1,050.00 | D | number of designation fees | amount of designation fee payable (maximum 10) | | 1,505.00 | I | 30.00 | P | 2,475.00 | TOTAL |
| first 30 sheets | 455.00 | b ₁ | | | | | | | | | | | | | | | | | | | | | | | |
| <u>0</u> x <u>\$0.00</u> | <u>0.00</u> | b ₂ | | | | | | | | | | | | | | | | | | | | | | | |
| remaining sheets additional amount | | | | | | | | | | | | | | | | | | | | | | | | | |
| 455.00 | B | | | | | | | | | | | | | | | | | | | | | | | | |
| 10 x 105.00 | 1,050.00 | D | | | | | | | | | | | | | | | | | | | | | | | |
| number of designation fees | amount of designation fee payable (maximum 10) | | | | | | | | | | | | | | | | | | | | | | | | |
| 1,505.00 | I | | | | | | | | | | | | | | | | | | | | | | | | |
| 30.00 | P | | | | | | | | | | | | | | | | | | | | | | | | |
| 2,475.00 | TOTAL | | | | | | | | | | | | | | | | | | | | | | | | |
| <p><input type="checkbox"/> The designation fees are not paid at this time.</p> | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p>MODE OF PAYMENT</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;"><input checked="" type="checkbox"/> authorization to charge deposit account (see below)</td> <td style="width: 33%;"><input type="checkbox"/> bank draft</td> <td style="width: 33%;"><input type="checkbox"/> coupons</td> </tr> <tr> <td><input type="checkbox"/> cheque</td> <td><input type="checkbox"/> cash</td> <td><input type="checkbox"/> other (<i>specify</i>): _____</td> </tr> <tr> <td><input type="checkbox"/> postal money order</td> <td><input type="checkbox"/> revenue stamps</td> <td></td> </tr> </table> | | | <input checked="" type="checkbox"/> authorization to charge deposit account (see below) | <input type="checkbox"/> bank draft | <input type="checkbox"/> coupons | <input type="checkbox"/> cheque | <input type="checkbox"/> cash | <input type="checkbox"/> other (<i>specify</i>): _____ | <input type="checkbox"/> postal money order | <input type="checkbox"/> revenue stamps | | | | | | | | | | | | | | | |
| <input checked="" type="checkbox"/> authorization to charge deposit account (see below) | <input type="checkbox"/> bank draft | <input type="checkbox"/> coupons | | | | | | | | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> cheque | <input type="checkbox"/> cash | <input type="checkbox"/> other (<i>specify</i>): _____ | | | | | | | | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> postal money order | <input type="checkbox"/> revenue stamps | | | | | | | | | | | | | | | | | | | | | | | | |

DEPOSIT ACCOUNT AUTHORIZATION (*this mode of payment may not be available at all receiving Offices*)

US is hereby authorized to charge the total fees indicated above to my deposit account.

- (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

07-1392

14 September 1999

Elizabeth Miller

Line 1 - Account Number

Rate of growth per month (year)

100-12016-100-REF005

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